UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,530	10/24/2000	Lars Wahlberg	19313-004 (NS-4)	4889

30623 7590 01/15/2003

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/696,530	Applicant(s) WAHLBERG ET AL.	
	Examiner Christopher Nichols, Ph.D.	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 42-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 42-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-23 and 42-56) in Paper No. 8 (12 November 2002) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The requirement is deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment of 12 November 2002 (Paper No. 8) has been entered in full. Claims 24-41 have been cancelled. Claims 1-23 and 42-56 drawn to $GFAP^+$ neuronal cell cultures and methods of making same, are under examination

3. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher James Nichols.

Information Disclosure Statement

4. The information disclosure statement filed 24 October 2000 (Paper No. 5) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Drawings

6. The drawings are objected to because Figure 2 appears to be skewed, missing some information. In addition, Figure 5 has two components. These should be label Fig 5A and 5B. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

7. The Specification is objected to because of the following informalities: spacing "function ," (pp. 2 line 9); handwritten correction (pp. 18 line 24); misspelled word "Parkinsonís" (pp. 19 line 6); two commas "TGF,," (pp. 26 line 4); spacing "the ,beta-" (pp. 28 line 25); spacing "and ,beta-" (pp. 29 line 16); delete comma after "i.e." (pp. 30 line 12 and line 20); spacing "maker ,beta-" (pp. 31 line 8); "GFAP0" should be "$GFAP^{+}$" (pp. 33 line 22); spacing "occasionally ,beta-" and "18 ."(pp. 33 line 27 and line 28); spacing "e.g.beta" (pp. 34 line 27); spacing "marker ,beta-" (pp. 35 line 24); capitalization "Meis2" (pp. 35 line 25); spelling "Br stle" (pp.

45 line 6); delete extra line after abstract "TRADCOS:1390742.2(tt3q02!.DOC)". Appropriate correction is required.

Claim Objections

8. Claim 9 is objected to because of the following informalities: claim 9 repeats "least". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-21 and 43-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated culture of GFAP+ cells wherein the proliferation-inducing growth factor is epidermal growth factor (EGF), does not reasonably provide enablement for any other proliferation-inducing growth factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 1-21 and 50-56 are drawn to an isolated cell culture of cells, which contains glia, and cells that can differentiate into GABA-ergic neurons with the withdrawal of serum and EGF. Claims 22-23 and

43-49 are drawn to method for producing a cell culture, which contains glia, and cells that can differentiate into GABA-ergic neurons with the withdrawal of serum and EGF.

10. The specification teaches that an NS4 cells is an undifferentiated neural cell that can be induced to proliferate using epidermal growth factor. NS4 cells have glial morphology and are immunopositive for both glial fibrillary acidic protein (GFAP) and nestin. Upon the withdrawal of serum and proliferation-inducing growth factors (such as EGF), NS4 cells differentiate into astrocytes ($GFAP^+$) and neurons (β-tubulin III^+).

11. The art teaches that undifferentiated progenitor cells differentiate into neuroblasts and glioblasts which give rise to neurons and glia, respectively. Growth factors, such as nerve growth factor, promote the growth and development of undifferentiated progenitor cells (US 6497872).

12. While general guidance is provided regarding isolation and preliminary characterization of NS4 cells, no working examples are provided re: all known proliferation-inducing growth factors.

13. Thus the claimed invention is to an isolated culture of NS4 cells and methods for isolating NS4 cells, which is not supported by the teachings of the specification or the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specific biological actions/activities that the proliferation-inducing growth factors would affect. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

14. Regarding proliferation-inducing growth factor, the art recognizes that "factor" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Due to the large quantity of experimentation necessary to identify all the applicable substances, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable proliferation-inducing growth factors, the absence of working examples directed to all known proliferation-inducing growth factors, the complex nature of the invention, the unpredictability of the effects of proliferation-inducing growth factors on cells (US 5766948; US 6497872; Santa-Olalla and Covarrubias, 1995), and the breadth of the claims which fail to recite limitations for what constitutes an applicable proliferation-inducing growth factor, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Claims 2, 4, 7, 44, 46, 48, 50, 51, 53, and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "majority" in claims 2, 4, 7, 44, 46, 48, 50, 51, 53, and 55 is a relative term which renders the claim indefinite. The term "majority" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the specification or the claims of the instant application to what percentage greater than 50% expressing the desired characerstic must be present before a "majority" of cells can be established.

16. Claims 18 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "some" in claims 18 and 21 is a relative term which renders the claim indefinite. The term "some" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the specification or the claims of the instant application to what number of cells expressing the desired characerstic must be present before a degree of "some" of the cells can be established.

17. Claims 1-23 and 43-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the terms "proliferation-inducing growth factor" and "differentiation-inducing culture conditions" are not adequately defined in the specification such that one of ordinary skill in the art could make or use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-23 and 43-56 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5753506 (19 May 1998). US 5753506 teaches an *in vitro* adhesion culture of CNS stem cells from a mammal (Col. 28 claims 6-12). US 5753506 teaches the isolation of a culture of CNS

mammal stem cells which are dissociated from the tissue, which can differentiate, are passaged frequently in the presence or absence of a growth factor, and can undergo controlled differentiation *in vitro* under serum-free conditions thus meeting the limitations of claims 1-6, 8-10, 12-14, and 17-18 (Col. 11 lines 27-67, Col. 12 lines 1-51). US 5753506 also teaches of a bipotential precursor cells which can differentiate in vitro into either a neuron or an astrocyte thus meeting the limitations of claims 1, 3, 20, and 21 (Col. 2 line 15-20). US 5753506 teaches that the isolated neural mammalian cell culture can differentiate into mature neurons that exhibit axon-dendrite polarity, synaptic terminals, and localization of specialized proteins for synpatogenesis and synaptic activity including neurotransmitter receptors, neurotransmitter transporters, and processing enzymes thus meeting the limitations of claim 21 (Col. 6 lines 60-67). US 5753506 teaches the use of epidermal growth factor in the culture medium of the cells thus meeting the limitations of claims 1, 3, and 16 (Col. 7 line 16). US 5753506 also teaches that the mammalian neural stem cell culture can be obtained from the striatum thus meeting the limitations of claims 11 and 50-56 (Col. 7 lines 28-33). US 5753506 teaches that the cells are nestin^{+}, GFAP^{+}, and express are GABA-ergic thus meeting the limitations of claims 1, 3, 7, 15, and 50 (FIG 1; FIG 8; Col. 14 lines 26-48). Although US 5753506 is silent on the absence of cortical (PAX6) and medial ganglionic eminence markers (NKX2.1) it is inherent that any cells derived from the striatum would be negative for cortical markers and that one all of the cells in the striatum are in the medial ganglionic eminence therefore, some, if not all, of the cells isolated by US 5753506 would be NKX2.1^{-}. Further, although US 5753506 is silent on the presence or absence of striatal markers (DLX1 and MEIS2) it is inherent in the art that cells derived from the striatum would be immunopositive for striatal markers. Although US 5753506 is silent on the

expression of vimentin by cells in the claimed culture, astrocytes express vimentin, especially actively dividing astrocytes such as astrocytomas (Rutka et al., 1999). US 5753506 teaches the isolation of a culture of CNS mammal stem cells which are dissociated from the tissue, which can differentiate, are passaged frequently in the presence or absence of a growth factor, and can under go controlled differentiation in vitro under serum-free conditions thus meeting the limitations of claims 22 and 23 (Col. 11 lines 27-67, Col. 12 lines 1-51). US 5753506 also teaches of a bipotential precursor cells which can differentiate in vitro into either a neuron or an astrocyte thus meeting the limitations of claims 22 and 23 (Col. 2 line 15-20). US 5753506 teaches that the isolated neural mammalian cell culture can differentiate into mature neurons that exhibit axon-dendrite polarity, synaptic terminals, and localization of specialized proteins for synpatogenesis and synaptic activity including neurotransmitter receptors, neurotransmitter transporters, and processing enzymes thus meeting the limitations of claim 23 and 43 (Col. 6 lines 60-67). US 5750376 teaches the isolation and characterization of a cell culture comprising nestin$^+$ and GFAP$^+$ cells thus meeting the limitations of claim 42 (Example 9: Proliferation of Embryonic Human Neural Stem Cells and Differentiation of the Neural Stem Cell Progeny; Col. 40 lines 20-25 and 35-40). US 5753506 teaches the use of epidermal growth factor in the culture medium of the cells thus meeting the limitations of claims 22 (Col. 7 line 16). US 5753506 also teaches that the mammalian neural stem cell culture can be obtained from the striatum thus meeting the limitations of claims 22 and 43-49 (Col. 7 lines 28-33). US 5753506 teaches that the cells are nestin$^+$, GFAP$^+$, and express are GABA-ergic thus meeting the limitations of claims 22, 23, and 43 (FIG 1; FIG 8; Col. 14 lines 26-48). Although US 5753506 is silent on the absence of cortical (PAX6) and medial ganglionic eminence markers (NKX2.1) it is inherent that any cells

derived from the striatum would be negative for cortical markers and that one all of the cells in the striatum are in the medial ganglionic eminence therefore, some, if not all, of the cells isolated by US 5753506 would be NKX2.1^{-}. Finally, although US 5753506 is silent on the presence or absence of striatal markers (DLX1 and MEIS2) it is inherent in the art that cells derived from the striatum would be immunopositive for striatal markers.

Summary

19. Claims 1-23 and 42-56 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
December 27th, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER